# EGFR

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# EGFR: Stopping Stathmin to Start the Cycle

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Hair follicles arise prenatally and directly begin to produce hair fibres as they undergo morphogenesis. In mouse skin, about two weeks after birth these follicles undergo synchronised arrest of cellular proliferation and enter a brief apoptotic phase (catagen), causing the follicle to regress into a resting phase (telogen). This first catagen marks the end of morphogenesis and the beginning of the adult hair cycle which will continue through life, with the duration of active growth (anagen) phases representing the principal determinant of hair length. In the mouse, the first two hair cycles are entered synchronously across the entire body, making this an excellent system to study hair cycle control, while later cycles are locally synchronised in a travelling wave that moves through the skin.

A number of diffusible signalling proteins and their downstream transduction pathways are known to be involved in hair follicle cycling *in vivo*, notably those of the BMP, FGF and WNT families. In particular, the well-studied telogen to anagen transition is controlled by opposing WNT/BMP signals that regulate the behaviour of the small population of bulge stem cells (1). Anagen entry, involving WNT activation, is followed by a defined period of growth that terminates in catagen. A wave of dermal BMP signalling then prevents the resumption of anagen, locking follicles for a period in telogen, until this wave passes and they are free to reacquire anagen-inducing signals (2). Cessation of anagen is achieved at least in part through reduction of WNT/β-catenin signalling (3) but no wave directly inducing catagen has been identified. In contrast to the telogen to anagen transition, which involves activation of a small group of stem cells, the shift from anagen to catagen involves the concerted die-off of a large number of epithelial cells, but this process has received less interest and a less complete picture exists. A particularly important question is how extracellular signals are linked to the cell proliferation and apoptotic machinery to achieve rapid changes in cellular state.

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Epidermal growth factor (EGF) has long been recognised as a hair cycle modulator and potent regulator of skin biology in a range of species (4), having been trialled in sheep for induction of shedding, as an alternative to mechanical shearing, through promotion of catagen and thus a break in hair fibre growth (5). In a recently published issue of *Experimental Dermatology*, Bichsel *et al* (6) address the mechanisms by which EGF signalling promotes catagen, using a mouse line with an epidermal deletion of the *Egfr* gene. They show that EGFR is activated by phosphorylation in epithelial cells across the morphogenesis-to-catagen transition and that *Egfr* mutated mice have a late and unsynchronised catagen entry, in contrast to the orderly switch in wild type mice. Using this model, they employ laser capture microdissection and expression profiling to determine follicular gene expression at 17 days of age, when control follicles are entering catagen while mutant persist in anagen. Comparison of gene expression profiles between genotypes identified altered expression of a rather large number of genes, to be expected in follicles on the cusp of such a profound change in physiological status. Among the genes with altered transcript levels were some associated with proliferation and apoptosis. Their detection of increased levels of *Rcc2* (encoding Regulator of chromosome condensation 2) led Bichsel *et al* to consider Stathmin as a candidate hair cycle regulator due to these factors being linked through Rac1 activation.

Stathmin is a tubulin binding protein that acts as a regulator of microtubule polymerisation with a particularly important role in cell proliferation (7). Stathmin is expressed in hair follicle epithelium during active morphogenesis, with levels normally falling as the transition to catagen begins, but, consistent with their morphological phenotype, Stathmin levels remained high in *Egfr*-deleted follicles. This observation suggests that EGFR signalling leads to a decrease in Stathmin levels. In their analysis of Stathmin mutant mice, Bichsel *et al* found that these enter catagen prematurely, and in an orderly and synchronised manner, precisely the opposite phenotype to lack of EGFR. Taken together, these findings suggest that EGFR activation leads to suppression of Stathmin function, thereby hastening catagen entry. It will be interesting to determine whether other catagen regulating signals, such as FGF5 (8), may also input to Stathmin to end the morphogenetic phase and usher in the mature hair cycle.

This advance helps to define how hair follicle cells balance proliferation and apoptosis to achieve hair cycle transitions. Further research focussing on the chain of events leading from EGFR to Stathmin would be particularly informative to illuminate the mechanisms underlying the sometimes conflicting and context-dependent outcomes of EGFR signalling. While in the lower hair follicle this signal shunts cells from proliferation into apoptosis, the sebaceous gland responds in a more complex manner (9). Bichsel *et al* note increases in sebaceous gland size in *Egfr*-deleted epidermis at certain stages, and detect corresponding alterations in the sebaceous gland gene expression signature, while previous reports identified enlarged sebaceous glands in mice with constitutively active EGFR (10). As EGFR promotes proliferation in the interfollicular epidermis, and in many internal organs in which EGFR is an oncogene and therapeutic target for suppression of tumour growth (4), further study of EGFR in the pilosebaceous unit is important to illuminate its dual nature in cellular proliferation and apoptosis.

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